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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,738	07/25/2001	Rainer Maurer	112843-006	5329

7590 06/10/2003
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EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/10/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,738	MAURER ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input checked="" type="checkbox"/> Other: <i>allowable subject matter</i> |

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The examiner acknowledges the Response filed on March 21, 2003 as paper No. 16. Amendments to the specification and claims have been entered as requested. Claims 1-6 are cancelled; new claims 7-12 are added. Claims 7-12 are pending in the application and are the subject of this Office Action.

DETAILED ACTION

1. Objection

The objections to the title and specification are withdrawn because of the amendments.

2. Rejections

2.1. 35 USC section 112, second paragraph

Rejection of claims 1-4 made in the previous Office Action, paper No. 15 is withdrawn because the claims have been cancelled.

Claims 7 and 11 are confusing in reciting "and a SEQ ID NO:1" which suggests that the full amino acid sequence of the enzyme is SEQ ID NO:1. It is suggested to amend the claim so that it included: "and comprises SEQ ID NO:1."

2.2. 35 USC section 112, first paragraph

3.2.1 Lack of written description

Rejection of Claim 6 made in the previous Office Action paper no. 15 is withdrawn, because the claim has been cancelled. However, new claims claim 7-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was

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not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a bromelain protease that has a molecular weight of about 24.4. KDa, an optimal activity at a pH ranging from about 4 to about 5.5 and comprises SEQ ID NO: 1. and to the use of said proteases in inhibiting of in blood coagulation.

The claims are directed to a genus of methods of use of bromelain proteases, whose characteristics are not sufficiently described. The claims are directed to any natural or man-made variants of bromelain proteases having molecular weight of about 24.4. KDa, an optimal activity at a pH ranging from about 4 to about 5.5 and a SEQ ID NO: 1. However, Applicants disclose only one species of genus, so called fraction F4, said species having the following identifying characteristics.

- (1) it originates from the *Ananas comosus*;
- (2) it has molecular weight of about 24.4. KDa, as measured by mass spectropscopy;
- (3) it has the optimum pH range of 4-5.5 when measured for the substrate which is L-pyroglutamyl-L-phenylalanine-L-leucine-p-nitroanilide (PFLNA);
- (4) its N- terminal amino acid sequence is that of SEQ ID NO:1;
- (5) it stimulates plasmin production;
- (6) it inhibits fibrin production; and
- (7) it inhibits adhesion of thrombocytes on endothelium cells.

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The specification fails to describe other species of the bromlain protease having molecular weight of about 24.4 KDa, an optimal acitivity at a pH ranging from about 4 to about 5.5 and a SEQ ID NO:1.

Because the disclosure fails to characterize other species of the claimed genus by identifying characteristics, one skilled in the art concludes that inventors had not possession of the claimed invention at the time the application was filed.

2.2.2. *Lack of enablement*

Rejection of claim 1-6 made under 35 U.S.C. 112, first paragraph, in the previous Office Action, paper no. 15, is withdrawn because the claims have been cancelled, and Applicant amended the disclosure to include the material incorporated by reference. The amendment is accompanied by the Affidavit in Support of Subject Matter Added to the Specification (Exhibit A). The affidavit is signed by Robert M. Barret, the Attorney of Record.

2.2.3. *Scope of enablement*

Claim 7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *Ananas comosus* stem protease isolated as fraction F4, does not reasonably provide enablement for any bromlain protease having molecular weight of about 24.4 KDa, an optimal acitivity at a pH ranging from about 4 to about 5.5 and a SEQ ID NO:1 wherein said protease can be applied for inhibition of blood coagulation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claim 7 is directed to a genus of methods for inhibition of blood coagulation comprising administering any bromelain protease that has molecular weight of about 24.4. KDa, an optimal activity at a pH ranging from about 4 to about 5.5 and a SEQ ID NO:1. Claim 11 is directed to medicament containing any such bromelain protease. The specification fails to disclose cloning and sequencing genes encoding proteases recited in claim 7 or 11, the procedures necessary as the first step in obtaining these proteases. Therefore, undue experimentation is necessary to make and use the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses proteases isolated from any plant of the family Bromeliaceae, as well as an enormous number of man-made variants thereof that would maintain the few characteristics recited in claims 7 and 11. Although cloning and sequencing genes is a very well developed field and skills of artisans are high, the experimentation required to make and use the claimed

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invention is out of the range of routine and tedious experimentation. The required experimentation includes:

- i) translating SEQ ID NO: 1 into the nucleotide sequences,
- ii) using the nucleotide sequences as primers in searching for the protease genes in the DNA of plants from the family Bromeliaceae,
- iii) expressing the candidate genes,
- iv) testing molecular weight, optimal pH of the expressed proteins,
- (v) selecting the ones having molecular weight of about 24.4 KDa, the optimal activity at pH ranging from about 4 to about 5.5,
- vi) testing the species selected above for use in inhibition of blood coagulation,
- (vii) further selecting those species that have inhibitory effect as recited in claims 8-10,
- (viii) transfecting the DNA molecules encoding the selected proteins into host cells, and
- (ix) producing the proteins required for use in the claimed medicament and treatment.

In addition, one skilled in the art is forced to construct any variant of the above protein that has the molecular weight of 24.4 KDa, pH range from about 4 to about 5.5, and comprising SEQ ID NO:1 at its terminus, wherein said variant has the protease activity the can be used for inhibiting of blood coagulation. This part of the scope

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requires an extensive DNA engineering and expressing that have a very low probability of success.

The disclosure is silent about any of the outlined steps and experimentation that are left to the skilled artisan. Without further guidance on the part of Applicants as to the sequence of the genes encoding protease of claim 7 and 11, as well as the species of the plant of the Bromeliaceae family to be used as a source of DNA, experimentation left to those skilled in the art is improperly extensive and undue.

2.3. 35 USC section 102

Rejection of claims 5 and 6 made in the previous Office Action, paper No. 15 is withdrawn because the claim have been cancelled.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Harrach et al. (Isolation and Partial Characterization of Basic Proteinases from Stem Bromelain, Journal of Protein Chemistry, 1995, Vol. 14, 41-52, included in IDS).

The claims are directed to a medicament, comprising a composition including a bromelain protease having molecular weight of about 24.4. KDa, an optimal activity at pH ranging from about 4 to about 5.5 and SEQ ID NO:1.

The bromelain protease having molecular weight of about 24.4 KDa, an optimal activity at pH ranging from about 4 to about 5.5 and SEQ ID NO:1 is fraction F4 of stem bromelain isolated, characterized and partially sequenced by inventors in the publication by Harrach et al. In particular, the same molecular weight is quoted by Harrach et al. on page 47, left column, line 10; the same optimal activity in the pH range of 4-5.5 is given

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by Harrach et al. on page 50, left column, line 5; the same amino acid sequence of SEQ ID NO:1 is given by Harrach et al in Table II, page 48.

In their response to the rejection of claims 5-6 under 35 U.S.C. 102(b), made in the previous Office Action, paper No. 15, Applicants write, "Applicants believe that patentable weight should be given to the preamble as claimed. In this regard, the medicament is for inhibiting blood coagulation" (page 8, line 26).

Applicants' arguments have been fully considered but are found not persuasive. The acting component of the claimed medicament is the enzyme disclosed in 1995, i.e., three years before the priority date of the instant application. The property of inhibiting of blood is the inherent feature of the said enzyme, therefore the medicament comprising as the active component exclusively said enzyme is not novel.

2.4. 35 USC section 103

Rejection of claims 1-4 under 35 U.S.C. 103(a), made in the previous Office Action, paper No.15, as being unpatentable over Harrach et al., (1995), and further in view of Taussig et al. (1988) is withdrawn in the light of Applicants arguments and because the claims have been canceled.

3. Conclusion

No claim is in condition for allowance, however the claims contain allowable subject matter. The following is examiner's reason for allowable subject matter.

Applicants disclose a method of use of a bromelain protease from *Ananas*

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coimodus stems for inhibiting blood coagulation. The protease stimulates plasmin production, inhibits fibrin production, and inhibits adhesion of thrombocytes on endothelium cells.

The closest prior art is the paper by Harrach et al. (Isolation and Partial Characterization of Basic Proteinases from Stem Bromelain, Journal of Protein Chemistry, 1995, Vol. 14, 41-52, included in IDS) which teaches the protease having molecular weight of about 24.4 KDa, an optimal activity at pH ranging from about 4 to about 5.5 and SEQ ID NO:1. The enzyme is isolated as fraction F4 isolated by Harrach from stem bromelain; see the above rejection under 35 USC 102(b). Harrach et al., however, do not teach that said protease has the property of

- (5) stimulating of plasmin production;
- (6) inhibiting of fibrin production; and
- (7) inhibiting of adhesion of thrombocytes on endothelium cells.

Thus, the method claimed is free of prior art and nonobvious.

As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

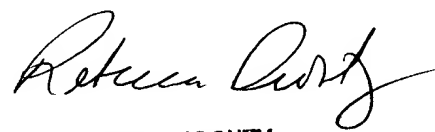
If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

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GROUP 122
1652